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Case Report
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Partial Ground Glass Nodule with Irregular Following-up "Rapidly" Progressed to Refractory Advanced Lung Cancer: A Case Report

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Abstract

A 62 years man was accidentally detected multiply GGN nodules and didn't do any following up examination. After suffering from a serious low back pain, he was diagnosed as right lung adenocarcinoma with metastases of hilar and mediastina lymph nodes, bilateral lungs, liver and multiple bones, IV stage, EGFR/ALK(-), STK11(+), MDM4(+). Because of intolerant to chemotherapy and other ways, he eventually died of respiratory failure in four months after confirmed diagnosis with total process was 39 months. Whether the rapid growth of mGGN is associated with hyper-progress mutations in KRAS combined with STK11 and MDM4 remains to be further studied urgently. According to the management guideline of Ground Glass Nodule (GGN), regularly repeated CT scan is extremely important to achieve early detection, diagnosis and treatment for lung cancer.

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Case Presentation

A 62 years man was accidentally detected four pulmonary nodules by low-dose computed tomography in April 5th, 2016 (Figures 1a-1d). He had 20 pack-years smoking history, no personal or family history of cancer, and didn't do any further examination. After suffering from a serious low back pain, chest-enhanced CT was performed in March 4th, 2019. The diameter of mixed Ground Glass Nodule (mGGN) in anterior segment of right upper lung was significant increased from 6 mm in 2016 (Figure 1b) to 13 mm × 10 mm in 2019 (Figure 2b, 2c), and it's density was completely changed into solid nodule. The pure Ground Glass Nodules (pGGN) respectively remained stable (Figures 1a-1d) and the solid nodule had disappeared (Figure 1c). Three newly pGGNs measuring diameter of 6 mm to 8 mm were found in the right lung (Figures 2f-2h). The solid nodule (SUVmax 3.6), group 4 and 11R lymph nodes (SUVmax 5.1), liver and multiply bone lesion with increased radioactivity (SUVmax 8.0) was significant obvious shown on the PET-CT (Figure 3, 4). CT-guided percutaneous needle biopsy for three lesions (solid nodule, pGGN and intrahepatic nodule) was performed on March 24th, 2019 (Figure 5). The results of histopathological were that no malignant cell was seen in pGGN on the left upper lung, malignant cell was seen both in solid nodule and liver lesion with CK(+), CK19(+), Ki-67 20%(+), CK7(+), CK8(+), CK18(+) (Figure 6). Molecular genetics detection result of solid nodule was KRAS, p.Gly12Val, abundance 9.57%; IDH1, p.Arg132Leu abundance 8.38%; SMARCA4, p.Gly11Val, abundance 3.56%; STK11, p.Asp194Tyr, 7.78%; TMB 20.6; MSS; and the result of liver lesion was KRAS, p.Gly12Val, abundance 16.54%; IDH1, p.Arg132Leu abundance 17.80%; SMARTA4, p.Gly1128* abundance 26.29%; MDM4 copy number amplification; TMB 17.5; MSS. In summary, he was diagnosed as right lung adenocarcinoma with metastases of hilar and mediastina lymph nodes, bilateral lungs, liver and multiple bones, IV stage, EGFR/ALK(-), STK11(+), MDM4(+). After the first-time chemotherapy with pemetrexed and Nedaplat, he refused to therapy again due to serious gastrointestinal reactions. Anlotinib was prescribed only for one week due to intolerance. Finally, he did not underwent any more treatment and eventually died of respiratory failure on July 21st, 2019.

Discussion

According to the Fleischner Society 2017 guidelines [1], mGGN ≥ 6 mm will be reexamined 3

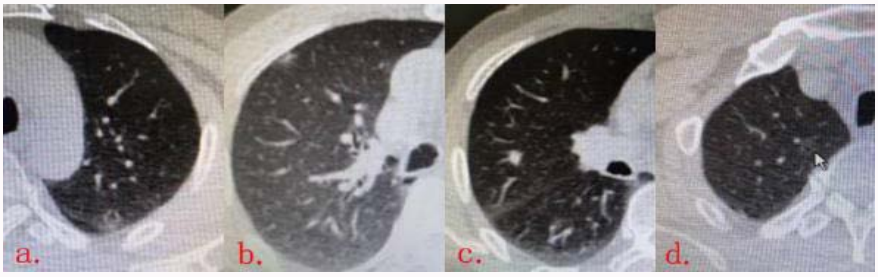

Figure 1: The CT images of pulmonary small nodules in 2016. (a) pGGN in apical or posterior segment of left upper lobe (13 mm). (b) part-solid GGNs in anterior segment of right upper lobe (6 mm, with solid components ≤ 4 mm). (c) Solid GGNs in posterior segment of right upper lobe (6 mm). (d) pGGNs in apical segment of right upper lobe (7 mm).

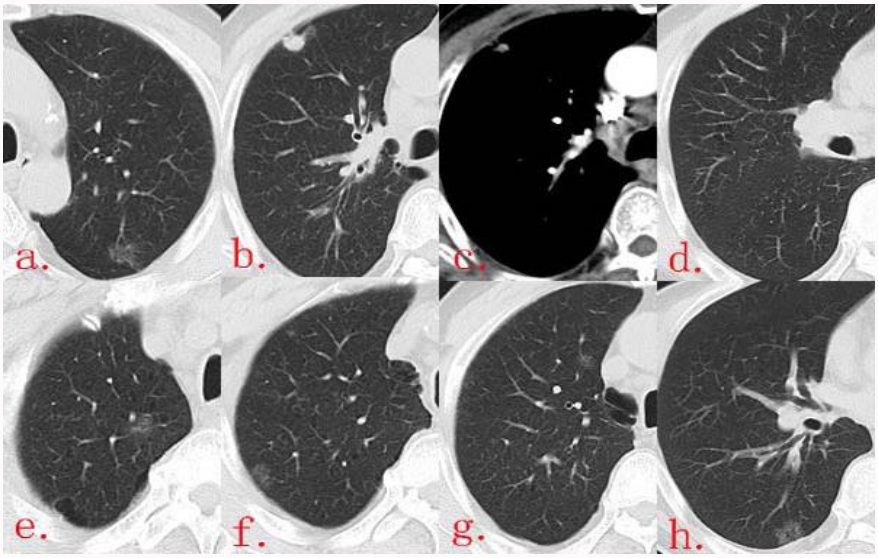

Figure 2: The CT images of Pulmonary Nodules in 2019.3. (a) pGGN in apical or posterior segment of left upper lobe (13 mm). (b) Solid nodule in anterior segment of right upper lobe (13 mm × 10 mm) in lung window. (c) Solid nodule in anterior segment of right upper lobe in mediastinal window. (d) Disappeared solid GGNs in posterior segment of right upper lobe. (e) pGGNs in apical segment of right upper lobe (7 mm) (f-h) New SSNs developed in apical segment of right lobes.

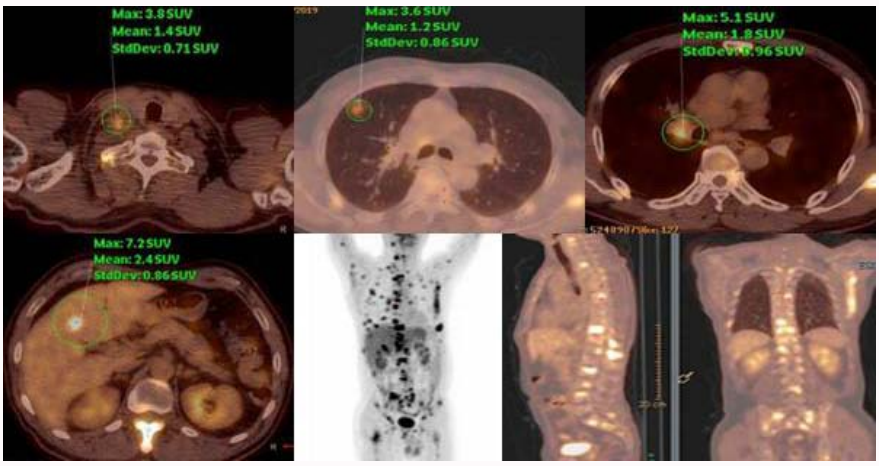

Figure 3: The result of PET-CT in 2019.

to 6 months after the first CT scan. If stable, repeated CT should be done annually for at least 5 years. This patient didn't do any following up CT scans until symptoms appeared. But in another aspect, it is known that persistent GGN exhibit very indolent growth features [2]. Based on the reports, for 16 AIS, the median VDT was 1240.3 days; for 3 MIAs, the median VDT was 1328.3 days; and for seven invasive adenocarcinomas, the median VDT was 941.5 days [3-5]. But the mGGN in this patient enlarged, became solid, progressed to advanced lung cancer less and to die only in 39 months. It's belongs to uncommonly rapidly progression. Why does his pGGN develop relatively quickly? Is it related to driver genes negative, intolerant to chemotherapy and the expression of immunotherapy super

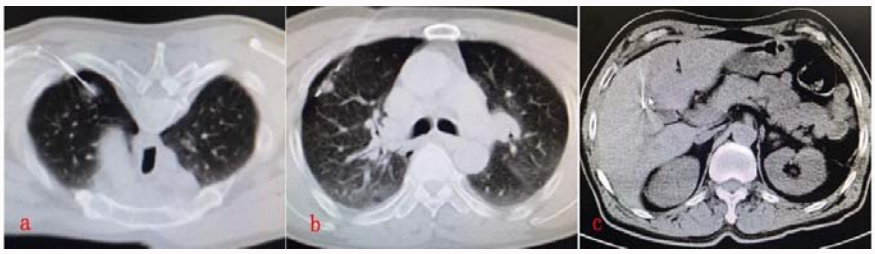

Figure 4: The images of CT-guided percutaneous needle biopsy. a. pGGN in left upper lobe b. Solid nodule in right upper lobe c. lesion in liver.

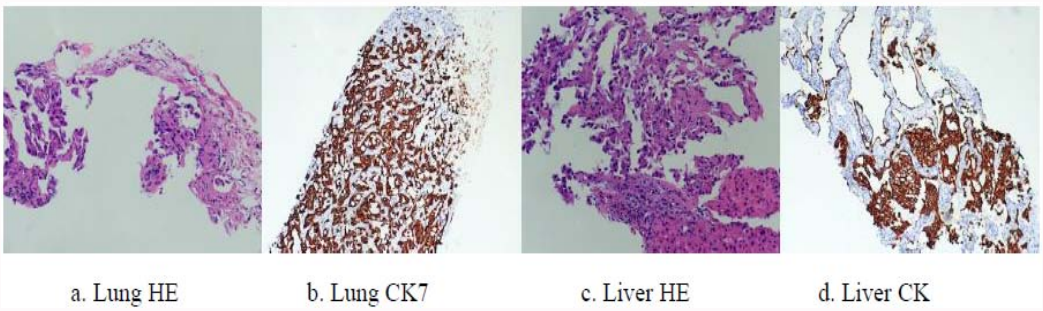

Figure 5: The results of Pathology and Immunohistochemistry.

progressive gene (STK11 and MDM4)? STK11 is a tumor suppressor gene encoding serine/threonine kinase 11, which is related to the differentiation, tumorigenesis, metastasis and immune drug resistance of lung cancer [6]. It is reported that STK11 inactivation mutations exist in 18% to 31% of KRAS mutated lung adenocarcinomas [7,8]. Kadara reported that mutations in STK11 were associated with poor PFS among KRAS-mutant tumors [9]. In 2017 ESMO congress, the team of Philip J. Stephens announced that patients with STK11 inactivation mutations had fewer infiltration of immune cells in their tumors and poorer efficacy of immunotherapy. On the other aspect, MDM4 is a homolog of MDM2 that interacts with it and also inhibits p53 tumor suppressor [10]. Shumei Kato et al. [11] recently reported that MDM2/4 alterations remained independent predictors of poor clinical outcome (TTF<2 months) with immunotherapies. Some patients with MDM2 family amplification had poor clinical outcome and significantly increased rate of tumor growth after single-agent checkpoint (PD-1/PD-L1) inhibitors. Whether the rapid growth of mGGN is associated with hyper-progress mutations in KRAS combined with STK11 and MDM4 remains to be further studied urgently.

Conclusion

According to the management guideline of Ground Glass Nodule (GGN), regularly repeated CT scan is extremely important to achieve early detection, diagnosis and treatment for lung cancer.

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